Specialty Conference

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Spectrum of Human Chlamydial Infections

PHYLLIS A. GUZE, MD:* The genus *Chlamydia* is one of the most widespread groups of organisms found in nature and is responsible for a large number of human infections.[1-3] These pathogens are causative agents of ornithosis (psittacosis), inclusion conjunctivitis, neonatal pneumonitis, lymphogranuloma venereum (LGV), genital tract and other infections.[3-5] In this symposium, we will review the clinical manifestations of the diseases associated with chlamydiae. Table 1 lists the diseases and associated serotypes for the human chlamydial agents. I will begin by discussing the microbiology of these organisms.

Microbiology

In the genus *Chlamydia,* two species are recognized: *Chlamydia psittaci,* which causes ornithosis (psittacosis), and *Chlamydia trachomatis,* which is responsible for most human infections including LGV, trachoma, inclusion conjunctivitis, neonatal pneumonitis, epididymitis, urethritis, cervicitis, pelvic inflammatory disease and other related diseases. *C trachomatis* strains are human pathogens with man as the sole natural host, whereas *C psittaci* strains appear to involve human diseases only as zoonoses.

The chlamydiae are obligate intracellular parasites that multiply by binary fission. The organisms contain both DNA and RNA but are unable to sustain growth outside an animal cell. They are susceptible to many antibiotics.[6-8] These organisms, therefore, have characteristics of both viruses and bacteria.

Chlamydial agents depend on the host cell for energy and metabolites. The life cycle is approximately 48 hours and very complex. An extracellular elementary body attaches to a host cell (columnar epithelium), induces phagocytosis and is ingested. Within the cell it reorganizes into a larger initial body (reticulate particle) that divides by binary fission, producing daughter cells. Division ceases after 18 to 24 hours and the initial bodies condense to form elementary bodies that subsequently rupture out of the host cell and infect other cells.[1]

C trachomatis is distinguished from *C psittaci*

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ABBREVIATIONS USED IN TEXT

CF = complement-fixation
CNS = central nervous system
IC = inclusive conjunctivitis
LGV = lymphogranuloma venereum
micro-IF = microimmunofluorescent
NGU = nongonococcal urethritis
PGU = postgonococcal urethritis
PID = pelvic inflammatory disease
VD = venereal disease

by the formation, in the former, of compact, rigid-wall, intracytoplasmic inclusions that contain glycogen and are stained by iodine.[9] *C psittaci* inclusions are diffuse and are not stained by iodine. In addition, *C trachomatis* is much more sensitive to sulfonamides than is *C psittaci*.[4]

The chlamydiae that cause trachoma and inclusion conjunctivitis were first isolated by inoculation of clinical specimens into the yolk sac of embryonated hens' eggs.[10] This time-consuming method has precluded its use clinically. Gordon and Quan[11] introduced a tissue culture method for isolating these agents using radiated McCoy cells and employing centrifugation of the inoculum to facilitate cell infection. Modifications of this procedure are in use today as routine techniques for the isolation of these organisms.[12-17] The major methods for showing inclusions in the infected cells are by iodine or Giemsa staining or by immunofluorescence. It is important that adequate tissue samples are collected in all attempts to isolate *C trachomatis*. For example, in nongonococcal urethritis, endourethral specimens are preferred to discharge specimens; urine and urine sediments have not been suitable.[12,18]

All members of the genus share a common group complement-fixing antigen. The group complement-fixation (CF) tests for serum antibodies are useful in the diagnosis of LGV and psittacosis[19] but not in the diagnosis of trachoma, inclusion conjunctivitis or the genital tract infections.[20-21] A microimmunofluorescent (micro-IF) technique[22] that serotypes *Chlamydia trachomatis* is most useful in the diagnosis of oculogenital infections and trachoma. There are 3 serotypes of the LGV agent and 12 serotypes of the trachoma-inclusion conjunctivitis agents.[1] Table 1 lists the diseases most commonly associated with specific serotypes.

Wang and Grayston[22] initially introduced the micro-IF test in 1970 for serotyping the organisms, but further studies from the same and other laboratories found it also to be a highly sensitive and specific indicator of antichlamydial antibodies.[4,23-27] The micro-IF test is more sensitive than the complement-fixation test.[25] The presence of a reaction in a single serum specimen simply reflects previous exposure. A changing titer may be seen in patients examined early in the course of infection—however, patients are seldom seen at this time. Unfortunately, many of the infections caused by *C trachomatis* are chronic and, although the micro-IF test can detect IgG and IgM antibody (presumed early infection), there is evidence that the IgM response may last for approximately a month following infection.[27] The micro-IF antibodies (IgG) may persist for life, although in some patients they disappear spontaneously.[27] Microimmunofluorescence may also be used to test secretions for antibody activity. Thus, the demonstration of antichlamydial antibody in tears may support the diagnosis of trachoma.[28,29] This test will probably be applied in the future to genital tract secretions.

A fourfold or greater rise in titer in either the complement-fixation or micro-IF test will support the diagnosis of chlamydial infection in the clinical syndrome being considered. Unfortunately, this is usually not observed, and often the clinician must simply use a single titer that has to be interpreted

TABLE 1.—*Human Diseases and Associated Serotypes Caused by* Chlamydia*

Species	*Disease*	*Serotype*†
C psittaci	Ornithosis (psittacosis)	Many unidentified serotypes
C trachomatis ..	Lymphogranuloma venereum	L-1, L-2, L-3
C trachomatis ..	Trachoma (hyperendemic)	A, B, Ba, C
C trachomatis ..	Inclusion conjunctivitis (adult and newborn), pneumonitis, nongonococcal urethritis, epididymitis, cervicitis, salpingitis, peritonitis and perihepatitis, infective endocarditis, pharyngitis, otitis	D, E, F, G, H, I, J, K

*Modified from Schachter.[3]
†Predominant, but not exclusive, association of serotype with disease.

in terms of the patient's disease and the background prevalence of antibody titers.[1]

Study of any natural chlamydial host shows a substantial degree of latent or inapparent infections.[2,30] The LGV agent can persist in the human host for many years because sequelae sometimes occur years after infection.[31] Acute trachoma may develop in persons who have left trachoma-endemic areas and have not had active disease since childhood.[32] Inclusion conjunctivitis, generally considered a self-limiting infection, has been shown to persist in some persons.[4,33,34] It is doubtful that chlamydiae persist in the host in a nonreplicating form. It is more likely that latent or subclinical infections represent persistent low levels of multiplication held in check by host defense mechanisms.[3]

DR. GUZE: *We will now review the variety of diseases caused by these agents. Dr. Bayer will discuss ornithosis (psittacosis).*

Ornithosis (Psittacosis)

ARNOLD S. BAYER, MD*

"ORNITHOPULMONARY" DISEASES are a well-defined group of clinical pulmonary disorders resulting from exposure to birds, their feathers or their excreta. These include several infectious diseases, such as cryptococcosis, histoplasmosis, avian tuberculosis, and the entity for discussion in this section, ornithosis (psittacosis). An additional avian-associated disease is the immunologically mediated "pigeon-breeder's lung" (bird fancier's lung). A partial list of birds known to carry infective agents that cause pulmonary disease is shown in Table 2.[35]

For purposes of nomenclature, "ornithosis" is a general term referring to any avian-related infection cause by *Chlamydia psittaci;* "psittacosis" (parrot fever) refers specifically to such infections related to psittacine birds (such as parrots, cockatoos, parakeets and budgerigars). I will use the general term ornithosis throughout this discussion.

Epidemiology

Ornithosis is a true zoonosis contracted by exposure to infected birds. Most cases are traceable to exposure to exotic, imported avian species.

TABLE 2.—*Ornithopulmonary Disease*

Disease	*Avian Genera Implicated*
Ornithosis (psittacosis)	Psittacine birds (parrots, cockatoos, parakeets) Nonpsittacine birds (pigeons, chickens, turkeys, ducks)
Cryptococcosis	Pigeons*
Histoplasmosis	Chicks, starlings, pigeons*
Avian tuberculosis	? Domestic birds and barnyard fowl

*Birds are not infected, but organism grows well in avian feces.

However, the disease is also recognized as a serious occupational hazard to people in the poultry trade, particularly in processing plants.[30,36] In such settings in the United States, turkeys are usually the type of bird implicated, while in Eastern Europe ducks have been the major source of industry-related ornithosis.[30] Also at risk for contracting ornithosis are pet shop personnel and people working in quarantine treatment centers for imported birds.

C psittaci causes natural infection of many avian species in the wild, but the chlamydial infection rate is relatively low.[37] However, as noted by Schachter,[3] there is an amplification of chlamydial infection that occurs by virtue of the crowding and stress involved in avian capture, shipping and quarantine. Therefore, newly imported birds represent a considerable health hazard to treatment center personnel and new bird owners. In the past, the United States depended on a system of chlortetracyline chemoprophylaxis given to birds in exporting countries before importation into the United States. This system was not satisfactory and has essentially been replaced by chlortetracycline prophylaxis administered to imported birds at US quarantine centers during their stay for Newcastle disease testing.[38] Unfortunately, there is no assurance that such preventive regimens are effective in eradicating *C psittaci* carriage. The failure of such an unsupervised program is evidenced by the recovery of the organism in avian excreta shortly after release from the US treatment centers.[39] In Germany, the unreliability of such a system has led to mandatory monitoring of chlortetracycline levels in birds given chemoprophylaxis before release from quarantine.[40]

It should be noted that *C psittaci* parasitizes the intestinal tract of lower mammals, as well as birds, and causes a variety of infectious syndromes in these animals including arthritis, pneumonitis,

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TABLE 3.—*Differential Diagnosis of Ornithosis (Psittacosis)*

Mycoplasmal pneumonia
Q Fever
Legionellosis
Primary coccidioidomycosis
Primary histoplasmosis
Viral pneumonitis

abortion, enteritis, conjunctivitis and encephalomyelitis.[2] However, mammalian-associated *C psittaci* infection is not considered a serious threat to humans as these strains are of relatively low communicability or pathogenicity for man.[3] The most frequent human infection with such strains is conjunctivitis, related to exposure to cats with "feline pneumonitis."[41]

Although *C psittaci* infection may be fatal in birds, only minimal evidence of disease is usually apparent.[42] The chlamydiae are found in avian body fluids and can be transmitted to humans by inhalation of aerosolized infected particles. This may be infected droplets, droplet nuclei or dust. Of interest, human-to-human transmission has been described. Physicians, nurses and other medical personnel caring for patients with ornithosis may acquire the disease; therefore, respiratory isolation techniques should be followed when such patients require admittance to hospital. *C psittaci* pneumonitis contracted from turkeys, psittacine birds or from an ill patient appears to be more severe than disease acquired from other sources.[43]

Pathogenesis

After exposure to a large *C psittaci* inoculum, the human host experiences nasopharyngeal monocyte-macrophage parasitization. The subsequent spread of the agent to the lungs and other extrapharyngeal sites is probably by hematogenous dissemination.[42] This is unlike lower respiratory viral infections where progression of infection is often from pharynx to lung by way of aspiration and contiguous cell-to-cell spread.[44,45] Other organ systems involved in the initial hematogenous dissemination are liver, spleen, cardiac and skeletal muscle, and the central nervous system (CNS).[43] These foci are also sites of several important extrapulmonary *C psittaci* clinical syndromes.

Clinical Syndrome

Clinically and radiographically, ornithosis closely resembles other "atypical" pneumonias, including those due to mycoplasmas, Q fever, Legionnaires' disease, influenza, other viruses, primary coccidioidomycosis and primary histoplasmosis (Table 3).[44-48]

The incubation period is approximately 7 to 14 days but may be shorter in large-inoculum transmission, as in human-to-human spread. Although variable, the clinical illness is generally biphasic, with an initial constitutional syndrome and a later pneumonitis syndrome. The constitutional phase is featured by moderate to pronounced extrapulmonary complaints of fever, chills, headaches, myalgia, photophobia and sore throat.[43] The fever is initially low grade (less than 38.9°C [102°F]) but usually becomes high (39.4° to 40.6°C [103° to 105°F] during the latter part of the first week of illness. Headache, photophobia and nuchal myalgia are often so prominent as to suggest meningitis, and this usually results in a lumbar puncture to rule out that possibility. Additionally, delirium, agitation and disorientation have been particularly emphasized in certain epidemics of ornithosis, again suggesting a primary CNS disorder. Epistaxis is seen in about 25 percent of patients in the constitutional phase of the disease.[42] Patients may also have primarily gastrointestinal complaints during this phase, especially abdominal pain, distension, nausea and vomiting.

During the latter part of the first week, after the onset of fever, pneumonic symptoms become prominent. As in other atypical pneumonias, a dry, hacking, nonproductive cough is characteristically noted.[46,49] Hemoptysis may occur in severe cases, especially in patients with tussive paroxysms. Other symptoms commonly seen with classic bacterial pneumonitis, such as purulent sputum, chest pain and pleuritic complaints, are infrequently observed.[50] Most patients are not dyspneic; however, in those with severe multilobar involvement, symptoms of acute respiratory insufficiency may develop.[42] A clinical corollary is that associated *C psittaci* myopericarditis should be considered in patients with documented chlamydial pneumonitis presenting in respiratory distress but for whom evidence of extensive pneumonitis *is lacking* on x-ray studies of the chest.[51]

On physical examination, most patients have high fever and tachycardia. Most patients will have a "temperature-plus dissociation"[43,49] or "relative bradycardia" as is seen in enteric fever, brucellosis and legionellosis.[52,53] As in other atypical pneumonias, pulmonary auscultation

usually discloses fine crepitant rales without signs of true consolidation.[46] It should be mentioned that the radiographic evidence of pneumonitis is frequently much greater than would be predicted by physical examination.[42] Splenomegaly is often prominent (10 percent to 70 percent of cases),[42] in contrast to other atypical pneumonias, and is an important differential feature. Approximately 25 percent of patients will have a faint macular eruption (Horder's spots) occurring during the constitutional phase of illness. These lesions blanch with pressure, are evanescent and located mainly on the torso, thus resembling the rose spots of enteric fever.[54] Occasionally, tender hepatomegaly and jaundice may be seen and mimic viral hepatitis. This is an uncommon yet prognostically ominous finding. A striking feature of ornithosis may be diffuse muscle tenderness on palpation, mimicking leptospiral or trichinotic myositis.[55,56]

A rare but severe complication of this disease is infective endocarditis.[57,58] The psittacosis agent generally infects previously abnormal or damaged valves on the left side of the heart. Psittacosis endocarditis generally requires an ablative surgical procedure for cure.

Routine Laboratory Studies

Routine laboratory evaluation is usually not helpful in distinguishing ornithosis from other infectious pneumonias, especially the atypical pneumonia syndromes. The leukocyte count is generally normal, commonly with lymphocytosis.[42] Examination of cerebrospinal fluid usually shows no abnormalities. Of diagnostic importance, serum cold agglutinins are rarely present. In contrast, cold agglutinins are present in approximately 60 percent of patients with mycoplasmal pneumonia,[59] a close clinical mimic of ornithosis.

Findings on x-ray studies of the chest resemble most atypical pneumonias:[46] Infiltrates are usually patchy and rarely lobar; "phantom" infiltrates are frequent, in which radiographic lesions disappear from one lung segment, only to reappear in another segment or opposite lung, and pleural effusions are uncommon. On rare occasions, miliary or nodular lesions have been observed on the x-ray films.[42]

Diagnosis

Confirmation of the diagnosis requires either isolation of the organism or demonstration of a significant rise in antibody. *C psittaci* is present in the blood during the constitutional phase and in both blood and sputum during the pneumonic phase of illness. Moreover, *C psittaci* persists in bronchial secretions for weeks after the onset of disease.[42] The organism can be isolated by inoculation of appropriate specimens into mice or into chick embryo yolk sacs.[60] As these techniques are not routinely available, the diagnosis is usually confirmed serologically. *C psittaci* and the agent of lymphogranuloma venereum share the same group antigens that form the basis of the complement-fixation assay. Sera should be tested during the acute and convalescent phases of illness to detect either a fourfold rise or fall in antibody titer. CF antibodies in this disease are generally present after the second week of illness. Any single positive CF titer ($\geq$1:16) in a patient with a febrile illness compatible with ornithosis is presumptive evidence of the diagnosis.[43,60] As is true when serological findings are positive in other infectious diseases, prompt initiation of appropriate chemotherapy may blunt antibody rise for several weeks or months into convalescence.[42,43,60] False-positive CF assays have occurred rarely in patients with Q fever or brucellosis.[43]

Therapy

The tetracyclines are the drugs of choice because the organisms are uniformly tetracycline-sensitive. *C psittaci* organisms are variably sensitive to the penicillins, erythromycin and chloramphenicol. Therefore, these drugs remain second-line agents in treating this disorder.[42,43]

Ornithosis is usually a mild disease, with abatement of fever and respiratory complaints occurring gradually over ten days to two weeks without specific therapy. Clinical relapse is rare. Introduction of tetracycline treatment (2 grams per day given orally in adults) usually shortens the febrile period by several days to a week.

Alternatively, ornithosis acquired from psittacine birds or from human-to-human spread tends to be clinically severe, with sustained or remittent fever and persistent respiratory symptoms for many weeks. In this setting, tetracycline therapy generally causes rapid lysis of fever within the first five to seven days. In severely ill patients, intravenously administered tetracycline (10 to 15 mg per kg of body weight per day) may be substituted for oral therapy. It is recommended that tetracycline therapy be continued for at least seven days after defervescence to prevent clinical re-

lapse.[61] It should be emphasized that radiographic resolution may lag several days to weeks behind clinical recovery.

The prognosis in ornithosis is good, with complete recovery the rule. The major morbidity and mortality are seen in the rare cases of chlamydial hepatitis, perimyocarditis or endocarditis.

Chlamydial Infections in Young Infants

BASCOM F. ANTHONY, MD*

CHLAMYDIAL CONJUNCTIVITIS in newborn infants (inclusion conjunctivitis or inclusion blennorrhea) has been appreciated for years as a common disorder, and the relationship of this entity to sexually acquired infection of the maternal birth canal was recognized long before characterization of the responsible agent (*C trachomatis* of the "oculogenital" serotypes, D through K). Two recent findings are largely responsible for a revival of pediatric interest in these infections. One is that perinatal acquisition of chlamydiae involves multiple organ systems in addition to the eye, and the other is that infection of the respiratory tract results in a distinctive and rather common form of pneumonia in young infants.

Epidemiology and Incidence

It is clear that the oculogenital chlamydiae are important causes of conjunctivitis and pneumonia in young infants. Recently, the simultaneous appearance of results from three prospective studies (Table 4) provides an estimate of the actual incidence of these infections.[62-64] Pregnant patients were surveyed one or more times during pregnancy for cervical infection with *C trachomatis,* and infants born to infected and uninfected mothers were followed for six months to a year. Follow-up involved clinical observations, chlamydial cultures and serological testing. The maternal infection rate varied from 2 percent to 9 percent, possibly due to differences in the populations or in diagnostic methodology. The follow-up data on infants of infected mothers are in remarkable agreement. In 33 percent to 44 percent, chlamydial conjunctivitis developed, in 11 percent to 20 percent chlamydial pneumonia occurred and in 16 percent to 20 percent there were asymptomatic chlamydial infections. Overall, in 60 percent to 70 percent of infants exposed perinatally, clinical or subclinical infection developed. By contrast, conjunctivitis was rare and other chlamydial disease was nonexistent in control infants born to uninfected mothers.

Other recent data suggest that, in addition to overt or symptomatic infection of the eye and respiratory tract, rectal and vaginal infection of newborns may be common.[62,65] It has also been suggested that chlamydiae acquired perinatally may play a role in serous and recurrent otitis media in young infants.[3,64]

Neonatal Conjunctivitis

Oculogenital chlamydiae are the most common specific cause of purulent conjunctivitis in newborns, but it is difficult to distinguish this clinically from other forms of neonatal ophthalmia. The symptoms usually begin at between 5 and 14 days of life but can appear earlier or later. Initial involvement is usually unilateral. In addition to a

TABLE 4.—*Prospective Studies of* Chlamydia *in Pregnancy and Infancy*

	Locale of Study		
	Denver[62]	*Boston*[63]	*San Francisco*[64]
Total number of women	340	322	900
No. positive (percent)	30(9)	6(2)	36(4)
Cultures/patient	2.3	1	1
Infants of positive mothers	18	6	20
Conjunctivitis (percent)	8(44)	2(33)	7(35)
Pneumonia (percent)	2(11)	1(17)	4(20)
Subclinical infection (percent)	3(16)	1(17)	4(20)
Total infected (percent)*	11(60)	4(67)	14(70)
Infants of negative mothers	16	89	18
Conjunctivitis (percent)	1(6)	3(3)	0

*Some infants had both pneumonia and conjunctivitis.

TABLE 5.—*Clinical and Laboratory Features of Chlamydial Pneumonia in Infants*

Onset	2 weeks to 2 months of age, usually insidious
Symptoms	Cough ("staccato"), tachypnea, nasal obstruction; usually mild
Physical findings	Afebrile rales, expiratory wheezes
Chest radiograph	Hyperexpansion, interstitial infiltrates
Laboratory findings	Eosinophilia, hyperimmunoglobulinemia

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purulent yellow discharge there are varying degrees of palpebral and bulbar inflammation and edema. Symptoms may persist or recur for weeks or months. Sequelae resembling those of trachoma are rare, but subtle changes (micropannus and conjunctival scars) apparent months or years later are relatively common.[62,66]

Chlamydial Pneumonia

The features of chlamydial pneumonia,[67-69] a fairly characteristic syndrome, are summarized in Table 5. The usual symptoms are tachypnea, staccato cough and nasal obstruction, beginning insidiously between two weeks and two months of age. Some infants have been symptomatic almost from birth and in a few, symptoms have developed in the third through fifth months of life. Fever is rare, the illness is generally mild, and many infants continue to thrive and grow normally. However, severe respiratory distress and apnea have been documented. Approximately half of the infants with this syndrome will have had conjunctivitis.[67]

When a physician is consulted (often after several weeks of low-grade illness), conjunctivitis may or may not be present. On examination, inspiratory rales are common and expiratory wheezes are variable. X-ray films of the chest show generalized hyperinflation of the lungs, scattered interstitial infiltrates and even areas of consolidation.

Certain readily available laboratory studies provide evidence that supports the diagnosis of chlamydial pneumonia. Eosinophilia is common, with absolute counts of 300 to 400 per cu mm or greater. Serum immunoglobulin levels are elevated, often to adult levels or higher. IgM and IgG are most consistently increased and IgA is often elevated.

Diagnosis

Specific diagnostic procedures are not yet widely available and usually require special arrangements. The definitive diagnosis of chlamydial infection in infancy is best made by isolation of the organism. If this is undertaken, direct scrapings or swabs of the conjunctival surface (rather than obtaining the exudate) or throat, or collections of nasotracheal secretions should be preserved in special medium pending transportation to a laboratory with the capability for chlamydial isolation.

Infants with conjunctivitis and pneumonia commonly demonstrate elevated antibody titers by micro-IF, but the serological diagnosis is complicated by passively acquired maternal antibody. Therefore, serial titers or testing for specific IgM antibody may be helpful. Showing chlamydial inclusions in conjunctival cells with Giemsa stain is a relatively sensitive and specific method for diagnosing chlamydial ophthalmia[3] and is widely available in clinical laboratories.

If specific diagnostic studies are unavailable or pending, it may be reasonable to institute antimicrobial therapy for a symptomatic infant whose illness is compatible with chlamydial pneumonia by clinical and laboratory criteria (eosinophilia and hyperimmunoglobulinemia).

Treatment

Neonatal chlamydial conjunctivitis is usually treated with topical tetracycline, sulfacetamide or erythromycin. Because of documented relapses and treatment failures with topical therapy,[70] and because of the likelihood that the conjunctival sac is only one of several body sites harboring *C trachomatis*,[65] two or three weeks of systemic therapy (erythromycin or sulfisoxazole) has been proposed.[70,71]

In an uncontrolled study of chlamydial pneumonia in infants, two weeks of systemic therapy with erythromycin (40 mg per kg of body weight per day) or sulfisoxazole (150 mg per kg of body weight per day) was associated with apparent eradication of chlamydiae from the respiratory tract and clinical improvement.[72]

Unresolved Questions

Recent new data on chlamydial disease have obviously expanded the role of these agents in certain common diseases of infancy. They have also raised questions about established procedures in the care of newborn infants. Because silver nitrate prophylaxis for gonococcal ophthalmia is apparently ineffective against chlamydiae, critics of Credé's regimen have an additional argument for an alternative, less irritating prophylaxis (topical tetracycline or erythromycin), which might prevent both infections. It should be pointed out that no regimen has been rigorously evaluated for the prevention of either chlamydial or gonococcal infection.

Although topical antimicrobial drugs are widely used for treating chlamydial conjunctivitis in newborns, this approach warrants reassessment vis-a-

vis systemic therapy (erythromycin or sulfisoxazole) in view of reported treatment failures with topical therapy and the probable desirability of clearing chlamydiae from other body sites in these infants.

The documentation of chlamydial disease in a young infant almost certainly indicates infection in the mother. Under these circumstances, it may be appropriate to recommend a therapeutic course of tetracycline in both parents.

DR. GUZE: C trachomatis *is the causative agent for lymphogranuloma venereum (serotypes L1-3) and other genital diseases (serotypes D through K). Dr. Tillman will discuss lymphogranuloma venereum, and I will then review the other male and female genital infections.*

Lymphogranuloma Venereum

DAVID B. TILLMAN, MD*

LYMPHOGRANULOMA VENEREUM (LGV) is a venereal disease (VD) caused by *C trachomatis*. It has also been called Durand-Nicolas-Favre disease, tropical bubo and lymphogranuloma inguinale. The infection involves primarily the lymphatics and lymph nodes of the genital area. Acute inguinal lymphadenitis is the most common manifestation. Late complications include strictures (rectal and urethral) and genital lymphedema. Although the disease was first described about 150 years ago, the causative agent was not isolated until 1940. Strains of *C trachomatis* isolated from patients with LGV show some biological differences from other strains of the organism. Of greatest clinical importance is an increased invasiveness and an affinity for lymphoid tissue rather than epithelial cells.[73]

Epidemiology

Although cases of LGV are found in most areas of the world, the greatest number occur in the tropical and subtropical areas of Africa and Asia. In the United States, LGV is endemic at a low rate and is seen primarily in the Southeast in blacks of low socioeconomic status. The disease is usually transmitted by sexual contact, but nonvenereal transmission has been reported following direct contact with infected tissues and fomites.[74] The frequency of transmission following sexual contact is not known. For unknown reasons, clinical infection is more common in males than in females.

Clinical Manifestations

A primary genital lesion occurs from three days to three weeks after exposure. It is a small, painless vesicle or ulcer located on either the penis or on the labia or vagina. It is noticed by less than a third of men and by even fewer women. It heals within a few days and is usually diagnosed retrospectively only when lymphadenitis appears.

From the site of primary infection the organism spreads by way of the lymphatics, and painful inguinal and femoral adenopathy occurs. The adenopathy is usually unilateral but can be bilateral. Progressive periadenitis leads to a matted mass of nodes that become fluctuant and suppurative. Enlargement of nodes above and below the inguinal ligament leads to the characteristic "groove sign," but this occurs in only a third of the cases.[75] Spontaneous healing eventually occurs. Constitutional symptoms such as fever, chills, headache, myalgias and arthralgias are common when regional adenopathy is present.

Primary anorectal infection occurs in women and homosexual men following anal intercourse. The organism infects intestinal epithelial cells and causes symptoms such as bloody or mucopurulent rectal discharge, tenesmus or diarrhea.

Early complications of LGV infection include bacterial superinfection, perirectal abscess and fistula formation. Late complications include rectal or urethral stricture and, uncommonly, elephantiasis of the penis or vulva.

Diagnosis

Although LGV is an uncommon disease, it is in the differential diagnosis of many common conditions such as inguinal lymphadenopathy, ulcerative genital lesions, perirectal abscess and fistula. At present, there are no entirely satisfactory ways to confirm or rule out the diagnosis of LGV. The best method is isolation of an LGV strain of *Chlamydia*. However, this method is positive only 30 percent to 50 percent of the time.[74] A complement-fixation test is available and is positive ($\geq$1:16) in 80 percent of cases. Unfortunately, it is not specific for acute infection because a

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rising titer is often difficult to demonstrate.[75] An intradermal skin test is commercially available, but it is not sensitive and is not currently used.[76] Micro-IF and counter immunoelectrophoresis tests have also been described. Both seem more sensitive and specific than older methods of diagnosis.[27,77]

Treatment

Treatment should consist of tetracycline, 500 mg taken four times a day for three to four weeks, or a sulfanamide, 1 gram taken four times a day for three to four weeks. Although this therapy will not cause early disappearance of a bubo, constitutional symptoms often disappear quickly. It is uncertain whether antibiotic therapy prevents late sequelae such as rectal strictures.

Male Genital Infections

PHYLLIS A. GUZE, MD

Chlamydia trachomatis IS A major cause of nongonococcal urethritis (NGU), postgonococcal urethritis (PGU) and epididymitis. Postgonococcal urethritis will be discussed with NGU.

Nongonococcal Urethritis

Nongonococcal urethritis is an extremely common sexually transmitted disease. In Great Britain, NGU is now at least three times as common as gonorrhea in men.[78,79] Although national statistics are not available in the United States, NGU is seen at least twice as often as gonorrhea in many venereal disease clinics[79,80] and private physicians' offices.[81] It is up to ten times more frequent than gonorrhea among men attending university health services.[81,82] Overall, it appears that NGU is at least two to three times as common as gonorrhea. Whereas gonorrhea is more common in homosexual males, blacks and persons of lower socioeconomic status, the frequency of chlamydial urethritis is higher than gonorrhea in whites, heterosexuals and persons of higher socioeconomic status.[83]

Evidence that 30 percent to 50 percent of cases of NGU are caused by *C trachomatis* has been substantiated by many groups.[84] Studies have repeatedly shown that *C trachomatis* can be isolated from the urethras of 30 percent to 50 percent of men who have NGU,[80,83,85-90] 20 percent to 30 percent of men with urethral gonorrhea,[80,83,85,91,92] and only 0 percent to 7 percent of men without urethritis.[80,83,85,87,88] Postgonococcal urethritis develops in 5 percent to 38 percent of patients with chlamydial-negative gonococcal urethritis, whereas this complication develops in approximately 80 percent to 100 percent of men with chlamydial-positive gonococcal urethritis (double infection).[85,89,92-94]

Clinical Manifestations

Generally, symptoms may be consistent with gonococcal urethritis: dysuria, urethral discharge or urinary frequency. Urinary frequency is rarely the only symptom.[95] NGU usually begins insidiously with a scant, watery discharge, although some patients have no discharge at the time of examination. The discharge is typically clear or white in color, thin and mucoid in consistency, and scant. Often it is demonstrable only after penile stripping.[96] In others, a copious purulent discharge is present. As many as 29 percent of patients with NGU are conscious of the discharge only in the early morning.[97] Female sexual partners of these men may give a history of acute or recurrent cystitis.[95] Prostatic enlargement and tenderness may be present.[98]

Diagnosis

The presence of urethritis should be confirmed by demonstrating an abnormal number of polymorphonuclear cells in the discharge[99,100] or in a first voided urine specimen.[83] Gonorrhea must be ruled out on the basis of Gram stain and culture. The identification of Gram-negative diplococci within polymorphonuclear cells correlates with the culture-positive diagnosis of gonorrhea in 98 percent of the cases, and failure to find the typical gonococcal organisms correlates with the diagnosis of NGU.[101] Establishing the cause of NGU as due to *C trachomatis* requires either cytologic diagnosis, chlamydial isolation or serodiagnosis.[1,102] Unfortunately, these tests are not routinely available.

Treatment

Patients with NGU should be treated with tetracycline, 250 to 500 mg four times a day for 7 to 21 days.[84,103-105] The exact length of time has not been established, although seven days is probably sufficient.[84,103] The dosage of 500 mg tetracycline four times a day for five days will also eradicate

Neisseria gonorrhoeae.[106] If tetracycline is contraindicated, erythromycin or sulfisoxazole for 14 days can be given.[5] The patient's sexual partners should also be treated.

If signs of urethritis persist, patient compliance must be considered, along with the possibility that not all sexual partners have been properly treated. About 70 percent of the female sexual partners of male patients with chlamydial urethritis have chlamydial infection of the cervix, and delay in treating these persons may lead to reinfection.[1,3,107] Additionally, other causes of NGU, such as *Trichomonas,* should be sought.

Epididymitis

A major role for *C trachomatis* in causing epididymitis was strongly suggested by the isolation of the agent from the epididymal aspirates of five of six men younger than 35 with "idiopathic epididymitis."[108] In this study, coliform organisms were responsible for epididymitis in the men 35 years of age and older. A prior study showed a significant rise in titer of chlamydial antibodies in two patients with acute epididymitis, which also suggested that *Chlamydia* is a cause of this disease.[109] Treatment is the same as recommended for NGU.

Female Genital Infections

PHYLLIS A. GUZE, MD

C trachomatis HAS BEEN isolated primarily from the cervix,[1,3,4,80,110-112] although organisms have also been recovered from the urethra,[12,86,113,114] upper genital tract[115,116] and peritoneal cavity.[117] I will arbitrarily divide the discussion of female genital tract infections into lower tract disease (cervix and urethra) and upper tract disease (salpingitis, pelvic inflammatory disease and peritonitis).

Lower Tract Infections

Cervicitis

Isolation of *Chlamydia trachomatis* from the cervix was first reported by Jones and co-workers in 1959.[118] Since that time a number of investigators have demonstrated chlamydial cervical isolation. Workers in this area have reported higher recovery of chlamydiae from women with cervicitis than from women with no abnormal findings.[110-112,119,120] The agent has been recovered from selected women with hypertrophic cervical erosions, mucopurulent endocervical discharges (mucopurulent cervicitis) and other cervical abnormalities.[111] However, approximately 5 percent of unselected women may be culture-positive without symptoms or cervical abnormalities.[121] So it appears that cervical infection with chlamydiae may range from asymptomatic disease through a spectrum of cervical abnormalities.

The symptoms observed in women with chlamydial infection are not distinctive and many women are asymptomatic. A structurally normal cervix is unlikely to be colonized by *C trachomatis*. However, the presence of higher grades of cervical discontinuity,* with or without purulent secretion, may indicate chlamydial infection, particularly if *N gonorrhoeae* and *T vaginalis* have been excluded as pathogens.[110]

The isolation of chlamydiae from normal cervices of asymptomatic women does not imply that these organisms do not act as pathogens. Indeed, the presence of these intracellular parasites means infection, at least at the cellular level. There is evidence that cervical infection can persist for many months,[112] and it is known that contacts of men with NGU have a higher incidence of chlamydial isolation.[80,111] It appears that chlamydial cervical infection may contribute to the high incidence of chlamydial NGU and is the basis for infection of neonates.

Diagnosis

Unfortunately, there are no specific signs or symptoms that specify *C trachomatis* infection. Several investigators have described a distinctive hypertrophic cervicitis with follicles that they feel are macroscopically characteristic of cervical chlamydial infection.[111,122,123] However, the validity of this finding is in question.[113] A history of NGU in the patient's partner is suggestive. There is a significant relationship between the presence of chlamydial antibodies in genital secretions and the isolation of chlamydiae,[124] but neither of these laboratory tests is readily available.

Treatment

The treatment schedules recommended for men with NGU are also applicable to women with

*Cervical discontinuity is a demarcated area usually spreading outwards from the external os, whose appearance differs from that of normal cervical epithelium.[110]

genital chlamydial disease. However, a 21-day course seems to be necessary for resolution of cervical abnormalities.[111]

Urethritis

A study of women contacts of men with NGU showed that 25 percent of the women excreted *C trachomatis* from the urethra only.[113] Urethral symptoms (burning, dysuria and frequency) were complained of much more often by those excreting *C trachomatis* from the urethra than by those excreting the agent from the cervix alone. A more recent prospective study implicated *C trachomatis* infection in 10 of 16 patients with the urethral syndrome who had sterile bladder urine and pyuria.[125] These studies suggest that *C trachomatis* may be a significant cause of abacterial urethritis in sexually active young women. Clarification of this issue awaits further studies.

Upper Tract Infections

Salpingitis and Pelvic Inflammatory Disease

The role of chlamydiae in diseases of the female genital tract, other than cervicitis, is just being elucidated. Eschenbach and co-workers[126] showed seroconversion in 15 of 74 women with pelvic inflammatory disease (PID) but recovered chlamydiae from the peritoneal fluid in only one patient. Mårdh and his colleagues[115] found that 30 percent of women with PID that they studied had chlamydial infection of the fallopian tubes as sampled at laparoscopy. A report by Paavonen and associates[116] showed that 26 percent of their study group with acute salpingitis were culture-positive for *C trachomatis,* and 43 percent of 72 patients from whom paired sera were obtained had either positive culture results for or seroconversion in the immunofluorescent test to *C trachomatis.* This seroconversion has also been documented in other work.[126,127] In the past, it was observed that in a series of mothers of infants with inclusion blennorrhea there would be some cases of PID. Currently, it is difficult to completely assess the role of chlamydiae conclusively in this disease, but it is likely that these organisms account for a proportion of cases of nongonococcal PID.

Diagnosis depends on culture isolation of *C trachomatis* from the fallopian tubes or cul-de-sac aspirate. Treatment has not been evaluated, but tetracycline has been recommended.[5]

Peritonitis

A possible role for *C trachomatis* in causing peritonitis and perihepatitis has been suggested by recent reports.[117,128] Muller-Schoop and co-workers[117] presented serological evidence of recent *C trachomatis* infection in 9 of 11 women who had acute peritonitis. Five of these patients had no evidence of gonococcal infection. Wolner-Hanssen and colleagues[128] reported four patients with peritonitis and perihepatitis, diagnosed by laparoscopy, who had positive cervical cultures only for *Chlamydia.* Chlamydiae seem to be plausible candidates for patients with nongonococcal Fitz-Hugh-Curtis syndrome.[117]

DR. GUZE: *Dr. Richard Bills will now discuss adult inclusion conjunctivitis and trachoma. I will finish this symposium with mention of some of the miscellaneous infections caused by chlamydiae.*

Adult Inclusion Conjunctivitis

RICHARD BILLS, MD*

ADULT INCLUSION CONJUNCTIVITIS (IC) is a follicular inflammation of the conjunctiva resulting from inoculation of the eye with genital secretions contaminated with chlamydiae. The infection clinically resembles the early inflammatory stages of trachoma but is associated with those strains of *C trachomatis* that cause genital infection (serotypes D through K) rather than the typical trachoma strains (serotypes A, B, Ba and C). Adult IC is primarily a disease of sexually active adults, the peak incidence occurring in the second and third decades.[129] The disease is almost always venereally transmitted either by direct oral-genital sexual activity or passive transfer of genital secretions to the eye. Reports of epidemics associated with potentially contaminated swimming pools do not rule out the possibility of venereal transmission and have been questioned.[1,130] Conjunctivitis is usually accompanied by concurrent genital infection (cervicitis, urethritis) in the patient or a sexual partner.[88,129] Unlike trachoma, eye-to-eye transmission is thought to be infrequent but accounts for reports of IC in elderly persons exposed to neonatal chlamydial conjunctivitis.[131] Although the disease has a worldwide distribution and vari-

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ations in geographic prevalence are suspected, documentation is unavailable. There does not appear to be an increased incidence in male homosexuals.[1]

Clinical Presentation

Experimental infection in human volunteers has shown an incubation period of 3 to 19 days.[132] Onset is acute with symptoms of tearing, burning, photophobia, a foreign body sensation and a slight mucopurulent discharge. Seventy percent of cases are unilateral. Ipsilateral, nontender, preauricular lymphadenopathy may be present. Examination at this stage shows hyperemia, papillary hypertrophy, superficial punctate keratitis with subepithelial corneal infiltrations and swelling of the limbal border. Typically, the inflammation is more severe on the inferior conjunctiva, but the entire mucosal surface may be affected. Serous otitis media occurs in a minority of patients and is usually asymptomatic.[133] Transient hearing loss has been reported.[134] Culture of middle ear aspirates for *Chlamydia* may be positive.[88] Follicular pharyngitis and anterior uveitis are uncommon findings.[1,135] Symptoms reach a peak by the third week, at which time ptosis and conjunctival lymphoid follicles are frequently seen. Without treatment the disease is generally self-limited with resolution over 3 to 12 months. Occasional patients demonstrate a less benign course. Inflammation continues and extensive corneal involvement results in scarring and neovascularization (pannus formation), with rare cases of visual impairment.[129,135] Severe IC is clinically indistinguishable from the later stages of endemic trachoma.

Diagnosis

A tentative diagnosis of adult inclusion conjunctivitis can be made clinically, but laboratory confirmation of *Chlamydia* as the cause is required. Definitive diagnosis is made by demonstrating the agent by morphology in tissue or growth in culture; serological testing is of limited diagnostic value.

A variety of laboratory techniques are available. Giemsa staining of conjunctival scrapings obtained during the acute phase shows a predominance of neutrophils with a scattered number of mononuclear cells. The diagnostic intracytoplasmic inclusions are scarce, and an experienced microscopist is needed for their correct recognition.[136] Scrapings have been positive in up to 60 percent of suspected cases when examined by experienced personnel.[88] Fluorescent antibody staining provides an even higher yield (80 percent) but is less specific.[137] Unlike endemic trachoma, there is rarely concurrent bacterial infection.[129] Growth of chlamydiae in tissue culture is possible using a variety of cell lines. Isolation is positive in 60 percent to 80 percent of suspected cases.[24,138] There is rough correlation between the degree of active inflammation and the ease of isolation of the organism in culture.[24]

Assays for antibody to chlamydial group antigen by complement-fixation are positive in 50 percent to 75 percent of culture-positive adults with conjunctivitis.[24,139] Type-specific serum antichlamydial antibodies (IgG and IgM) are detectable by micro-IF techniques in virtually 100 percent of patients,[138,140] but they are also positive in 24 percent to 40 percent of unaffected normal adults and 60 percent of patients in a metropolitan VD clinic.[129] Rising titers are found only occasionally with adult IC as genital infection usually precedes ocular involvement, and the serological response has already stabilized when the conjunctivitis develops. In general, serological testing has limited usefulness. Identification of antichlamydial antibodies (IgG and IgA) in tear specimens is more specific for ocular infection but is not widely available.[29,102,141]

Differential Diagnosis

Inclusion conjunctivitis must be distinguished from other forms of acute follicular conjunctivitis. The major differential entities are adenoviral conjunctivitis and herpes simplex keratoconjunctivitis. Differentiation is usually apparent by the shorter course of viral conjunctivitis (one to three weeks), the predominance of mononuclear cells in conjunctival scrapings and the findings on slit-lamp examination (for example, dendritic corneal ulcer). Viral isolation is the definitive diagnosis.

Treatment

The treatment of choice for adult IC is systemic tetracycline (1 to 2 grams per day for three weeks) or erythromycin (1 gram per day for three weeks).[139,142] Response is prompt with resolution of symptoms within 48 hours. Several months may be required for resolution of lymphoid follicles and corneal opacities.[1,137] Cultures become negative within 24 hours of initiation of therapy. Cytologic findings from scrapings may remain positive for several days.[138]

Topical antibiotics may diminish symptoms but

do not eradicate the organism.[139] Topical steroids prolong the course and have been associated with worsened inflammation on discontinuation.[139] Neither is recommended. Resistant infections are usually the result of reinfection rather than resistant organisms or relapse. It is essential to treat all sexual contacts with the same antibiotic regimen if reinfection is to be prevented.

Trachoma

RICHARD BILLS, MD

TRACHOMA IS A chronic inflammatory disease of the conjunctiva and cornea, which continues to be the most common cause of preventable blindness in the world today.[137] The disease was widespread in the Mediterranean basin in antiquity and became epidemic in Europe following the return of the French troops from the Egyptian campaigns under Napoleon. Improved sanitation and standards of living during the past 100 years have essentially eliminated trachoma in developed countries. It remains endemic in northern Africa, the Middle East, India and Southeast Asia. In North America, small endemic pockets of trachoma are still present among southwestern Native Americans.[32,143]

Pathogenesis

Endemic trachoma results from conjunctival infection with serotypes A, B, Ba and C of *C trachomatis*. Total Ba is most frequently isolated from Native Americans.[4] The organism is transmitted from person to person by direct contact with infected conjunctival secretions.[144] Hands, contaminated clothing and towels, and flies or gnats which feed on the eye discharge are felt to serve as important vectors.[135] Transmission is facilitated by conditions associated with poor sanitation, unavailable household water supply and environmental crowding.[130]

Intensive studies of endemic trachoma in Tunisia[144,145] and Taiwan[146] have shown that infection is acquired early in life and active disease is most prevalent in children younger than 10 years old. In certain communities virtually all children are infected by 2 years of age. The prevalence begins to decline by 5 years of age and reaches a stable rate of less than 5 percent of active inflammatory disease in adults.[144] However, conjunctival scarring continues into adulthood even as active inflammation wanes with adolescence.

Clinical Presentation

Symptoms of the initial infection may include a burning or foreign body sensation and a moderate mucoid discharge without systemic symptoms. Examination shows a nonspecific follicular conjunctivitis principally affecting the upper tarsal plate. There is a mixed neutrophilic and mononuclear infiltrate of the conjunctiva and variable papillary hypertrophy. Aggregates of lymphocytes with germinal centers known as conjunctival follicles appear as grey-yellow avascular elevations measuring 0.2 to 2 mm in diameter. If there is no recurrence of the infection, the evolution of the disease resembles that of adult inclusion conjunctivitis, with seroconversion and complete healing over the course of a year without specific therapy.[146] Reinfection is inevitable in endemic areas, however, and most children have continued active inflammation.[137]

As the disease progresses, scarring of the conjunctiva occurs. Initially, there may be only fine linear scars on the upper tarsal plates, while confluent areas of fibrosis are found in severe cases. Several authors[137,147] have suggested that conjunctival follicles and progressive scarring result from the host's hypersensitivity to chronic chlamydial antigenic stimulation during reinfection.

Involvement of the bulbar conjunctiva characteristically begins at the superior margin of the globe, with subepithelial inflammatory infiltrates (punctate keratitis) progressing to fibrosis and neovascularization of the mucosal surface. The resulting fibrovascular membrane (pannus) extends to the limbus and eventually involves the cornea itself.[139] There is swelling of the limbal border with circumferential lymphoid follicles. Regression of these follicles with scarring results in small depressions surrounding the cornea (Herbert's pits) that are pathognomonic. Corneal involvement typically begins at the superior border, but eventually all meridians are involved. Rarely is the pannus extensive enough to cover the pupil or obscure vision.[137]

Blindness occurs in adults and results from the sequelae of lid distortion combined with secondary bacterial infection.[135] Progressive conjunctival scarring during adulthood causes distortion of the tarsal plates with inward turning of the eyelids (entropion) and the eyelashes (trichiasis). The misdirected eyelashes constantly abrade

the corneal surface, resulting in superficial ulcerations that frequently become superinfected by bacteria. *Hemophilus* sp and *Moraxella* sp are the most common ocular bacterial pathogens in trachoma-endemic areas, occurring as epidemics of purulent conjunctivitis in the spring and summer.[145]

The combination of repeated corneal trauma, progressive scarring of the mucosal surfaces and superimposed bacterial infections contribute to the visual loss.[135] The damage is further exacerbated by fibrosis and occlusion of the lacrimal duct, with development of the "dry eye syndrome."[137] Blindness is extremely rare before the age of 30, even in hyperendemic areas.[144] Continued scarring of the conjunctiva and cornea can be seen as long as 20 to 40 years after cessation of active inflammation at a time when the chlamydial pathogens are no longer demonstrable by laboratory means.[142]

Diagnosis

In 1962 the World Health Organization published criteria for the diagnosis of trachoma.[148] Diagnosis can be made if two of the following clinical features are present: lymphoid follicles on the upper tarsal plate, typical conjunctival scarring, vascular pannus or limbal follicles or their sequelae, Herbert's pits. While such guidelines are useful for epidemiological surveys in endemic areas, they do not address the early stages of active inflammation. Laboratory confirmation of the clinical diagnosis is required during early stages to differentiate trachoma from other forms of chronic follicular conjunctivitis. This is accomplished by morphological identification of the organism in tissue, by culture or by rising serological titers.[149] The various techniques are discussed in the section on adult inclusion conjunctivitis. Endemic trachoma, however, presents unique diagnostic features. Conjunctival scrapings are positive for typical inclusions in less than 10 percent of adult patients by Giemsa staining and in 20 percent to 50 percent by fluorescent antibody staining.[21,150] Studies have shown that the ease of demonstration of the organism in scrapings has a rough correlation with the degree of active inflammation[21,102] and the endemicity of trachoma within the community.[24] Scrapings have a low yield in adults with little active inflammation and in the scattered areas of endemicity in North America.

Complement-fixation titers for chlamydial group antigens are positive ($\geq$1:16) in approximately 20 percent of affected patients,[21] while micro-IF titers are positive (>1:8) in up to 70 percent.[24] It must be emphasized that these serological results only document prior exposure and do not provide definitive evidence of current infection.

Although culturing of the organism is possible from trachoma patients, it is of little practical use in most rural endemic areas.[136] Culture techniques have been employed in studies of Native Americans, but the yield has been low.[143] In general, diagnosis in endemic areas has relied on Giemsa staining or, more recently, fluorescent antibody staining of scrapings combined with typical clinical findings.

Differential Diagnosis

The clinical diagnosis of trachoma in the later stages is seldom difficult. Early disease, however, presents as a nonspecific follicular conjunctivitis. The differential diagnosis includes toxic follicular conjunctivitis resulting from chronic exposure of the eye to foreign substances (such as cosmetics or medications), allergic keratoconjunctivitis, bacterial conjunctivitis and Parinaud's oculoglandular syndrome. The latter has multiple causes including sarcoidosis, tularemia, secondary syphilis and cat-scratch disease. In each of these entities, unlike trachoma, the disease is sporadic rather than endemic within the community. A careful history, consideration of the epidemiological setting, appropriate cultures and serological testing will differentiate early chylamydial infection from these other forms of conjunctivitis.

Treatment

The failure to eradicate trachoma in endemic areas is a function of the inability to break the cycle of reinfection. Trachoma is a disease of poverty and its corollaries, crowding and poor hygienic conditions. Infection confers no immunity, and reinfection is inevitable in endemic areas unless there is improvement in the standard of living. It has been shown repeatedly that improvement in the economic and public health conditions reduces the prevalence and severity of trachoma within an endemic community.[144] No regimen using antibiotics alone has been successful.

Several antibiotics are available for topical and systemic therapy of trachoma.[7] Tetracycline, erythromycin, sulfonamides and rifampin have all been effective in population studies.[7,139,141,151,152]

Eradication programs must be directed specifically at school-aged children as they constitute the principal reservoir of the organism. Ideally, the whole community is treated. Orally given antibiotics are generally more successful than topical therapy.[151] Suggestive regimens include 2 to 4 grams of tetracycline or erythromycin taken orally each day for three to four weeks,[143] or tetracycline ointment three to four times a day for four to six weeks.[139] Intermittent, prolonged topical therapy (five days per months for six months) has also been successful.[139] With these therapies there is an improvement in the clinical activity of inflammation, reduction in ocular bacterial pathogens and variable reduction in density of organisms shown by fluorescent antibody staining of conjunctival scrapings.[143,145] As expected, suppression of disease is only temporary in hyperendemic, underdeveloped areas. Mass treatment has been most successful when associated with economic expansion, as has occurred in Taiwan. Topical steroids should not be used.[139] Prevention of blindness in adults also involves surgical correction of lid deformities and treatment of bacterial superinfections.[135]

Attempts to develop an effective vaccine against *C trachomatis* have been unsuccessful. Vaccines using a variety of antigenic preparations have produced only transient resistance to infection and a modest reduction in the intensity of established disease.[4,139] In addition, more severe inflammation may develop in vaccinated patients when rechallenged with the organism, presumably a result of induced hypersensitivity.[4]

Miscellaneous Infections

PHYLLIS A. GUZE, MD

Endocarditis

CULTURE-NEGATIVE ENDOCARDITIS due to *C psittaci* has been documented in the literature.[57,153,154] In two patients, the infection occurred on previously damaged valves and both patients died.[153] In one patient, urgent aortic valve replacement was necessary.[57] A more insidious course with subsequent mitral valve replacement was reported in the other case.[154]

Recently, a fatal case of culture-negative *C trachomatis* endocarditis in a young woman with a previously normal aortic valve was reported.[155] The retrospective diagnosis was made by detecting a 32-fold rise in the patient's IgM antibody using the micro-IF technique and by ultrastructural examination of the necropsy tissue. This is the first association of endocarditis with *C trachomatis*. Both *C psittaci* and *C trachomatis* should be considered in the differential diagnosis of infective endocarditis with negative cultures of blood specimens.

Reiter's Syndrome

It has been suspected for several years that chlamydial infection may be associated with Reiter's syndrome. *C trachomatis* has been isolated from the urethra, conjunctiva, synovial membrane or synovial fluid of patients with Reiter's syndrome,[1,156,157] and evidence for the frequent association of chlamydial infection with this syndrome has recently been presented.[158] In the genetically predisposed host, chlamydiae may be one of several agents that may initiate or make these patients more susceptible to the development of this syndrome.[1,159] Treatment of *C trachomatis* infection will relieve the infectious symptoms but will not reliably relieve the other manifestations of Reiter's syndrome.[5]

Other Infections

Chlamydial agents have been associated with *pharyngitis* in adults with inclusion conjunctivitis[160] and in one patient without ocular involvement.[161] *C trachomatis* has also been recovered following myringotomy of a patient with *otitis* and conjunctivitis,[162] and *hearing loss* has been documented.[134] Isolation of this agent from the *lower respiratory tract* of six adult patients who had pulmonary infection now raises the possibility of *C trachomatis*-associated respiratory disease in the adult.[163] Schachter[1] states that a simplistic approach may be to assume that any anatomic site containing columnar epithelial cells may be susceptible to chlamydial infection and disease, if a means of transmission exists.

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